## REMARKS

Claims 1-5 were pending. Claim 1 is amended herein. The amendment finds support in the specification as originally filed (*see, e.g.*, specification at paragraph 0062). No new matter has been introduced by this amendment. As such, Claims 1-5 are pending.

### Double Patenting Rejections

Claims 1-5 have been rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over U.S. Patent No. 6,525,242 – the parent of the instant application – in view of U.S. Patent Application No. 2001/0007153. A terminal disclaimer is submitted herewith. Applicants note that the filing of this disclaimer is not an admission of the propriety of the rejection of these claims. *See Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870 (Fed. Cir. 1991). As such, Applicants respectfully request that the rejections of double patenting be withdrawn.

### Rejections Under 35 U.S.C. § 102(e) in view of Brown

Claims 1-5 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Application No. 2001/0007153 A1 to Brown et al., filed June 16, 1997 ("Brown"). Applicants respectfully disagree.

Concluding that "the claimed invention is disclosed in the prior art," the Examiner reasons that:

> Brown et al. discloses a non-human animal model having incorporated therein a solid chimeric organ in a manner such that the animal, previously

> incapable of supporting a viral or pathogenic infection, becomes susceptible to infection. The reference teaches that it is particularly desirable to make animals that support a Hepatitis C infection (see paragraph 0038). The reference specifically teaches that, in the absence of stimulation, intrasplenic injection of hepatocytes can create a chimeric liver with approximately 1% of the hepatocytes derived from an allogeneic or xenogeneic donor (paragraph 0039). The reference further teaches that a higher representation of donor cells may be achieved by administration of compounds that are hepatotoxic, such by D-galactosamine, carbon tetrachloride, and pyrrolizidine alkaloids (paragraph 39). The reference teaches inducing immunotolerance by specific suppression of an immune reaction (paragraphs 0043 and 0044). The reference specifically points out that the same allogeneic or xenogeneic source used for the implantation can be used as a source for the tolerization as well and that, although intact hepatocytes are needed for the implantation, lysates of cells have been found to be as effective as whole cells for induction of tolerance (paragraph 0044). The reference specifically teaches using the HuH-7 cell line (paragraph 0092).

(Office Action at pages 3-4).

Applicants assert that Brown does not anticipate the claimed invention, which requires that the invention be described in sufficient detail. *See, e.g., Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989) ("Every element of the claimed invention must be literally present, arranged as in the claim. The identical invention must be shown in as complete detail as is contained in the patent claim."). Indeed, Brown's disclosure relating to non-immunocompromised animal models for liver disease appears to be nothing more that "a mere wish or plan for obtaining the claimed [ ] invention." *Regents of Univ. of Calif. v. Eli Lilly and Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

In addition, Applicants submit that the superficial disclosure of non-immunocompromised animal models in Brown would not enable one of ordinary skill in the art to practice the instantly claimed invention. Given the paltry disclosure on the

methods required to actually make such non-immunocompromised animals having human chimeric livers, Brown not surprisingly practices only immunodeficient animal models (*i.e.*, RAG-2 mice; *see* Brown at Example 1 on page 11). Indeed, Brown's immunodeficient animals were much more laborious to create than it would have been to follow their own disclosure regarding non-immunocompromised animals, likely indicating that such disclosure was not enabling even for its authors.

Thus, it is respectfully submitted that unlike Applicants' extensive disclosure on non-immunocompromised animals, Brown's prophetic and generic reference to chimeric liver model systems in animals having an intact immune system (Brown at paragraphs 0043-0044) lacks sufficient disclosure to enable a person of ordinary skill in the art to make and use such animals.

Moreover, despite the Examiner's assertion that "[t]he reference specifically teaches using the HuH-7 cell line" (Office Action at page 4), such hepatocytes are mentioned only once in the specification (at paragraph 0092) and only in the context of their use as a control to test for the ability of another immortalized line to form tumors in the immunocompromised mouse, RAG-2. This disclosure, therefore, cannot anticipate, and indeed has no bearing on, Applicants' novel animal model having a normal immune system and a chimeric liver containing Huh7 cells.

Accordingly, when properly considered, Applicants assert that Brown is not an enabling disclosure and therefore, respectfully request withdrawal of the rejections of Claims 1-5 under 35 U.S.C. § 102(e) in view of Brown.

**Rejections Under 35 U.S.C. § 102(e) in view of Vierling**

Claim 1 has been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,034,297 to Vierling, filed September 26, 1997 ("Vierling"). Applicants respectfully disagree.

Applicants respectfully assert that the Examiner's conclusion that "one of skill in the art would understand the term 'tolerant' to encompass general immunosuppression" (Office Action at p. 4) is neither supported by evidence nor by the instant specification. Although the Examiner admits "the specification states that the term 'tolerant' does not refer to a state of general immunosuppression," it is reasoned that "[this] interpretation [ ] is not the conventional understanding in the art [and] [t]hus, the term tolerant is construed to broadly encompass general immunosuppression as well as specific immunosuppression." (Office Action at p. 4).

It is well settled in the patent laws that the applicants are their own lexicographer. *See, e.g., Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 951 (Fed. Cir. 1993) ("Although a patentee can be his own lexicographer, as we have repeatedly said, the words of a claim will be given their ordinary meaning, unless it appears that the inventor used them differently.) (emphasis added). *See also Process Control Corp. v. Hydreclaim Corp.*, 190 F.3d 1350, 1357 (Fed. Cir. 1999) (despite resulting in a non-operative claim, the Court held that "[w]here, as here, the claim is susceptible to only one reasonable construction, the canons of claim construction cited by [patentee] are inapposite, and we must construe the claims based on the patentee's version of the claim as he himself drafted it.").

In this case, the Examiner's understanding of the claim term "tolerant" clearly has improperly replaced the Applicants' explicit definition of the claim term:

> The term "tolerant", as used herein, does not refer to a state of general immunosuppression (as might be achieved, for example, by treatment with cyclosporine, or as may exist in an animal with a generalized B cell and/or T cell deficiency) but rather indicates a state of antigen-induced non-responsiveness of lymphocytes achieved by clonal deletion, cell-mediated suppression, or anergy (see, for example, Davies, 1997, "*Introductory Immunobiology*", Chapman & Hall, London, p. 366) directed specifically toward the introduced human cells.

(Specification at paragraph 0062). Only under the Examiner's newly conceived and impermissibly broad construction of the term "tolerant" does Vierling have any relevance to the instantly claimed invention. The Examiner admits that Vierling teaches only scid/scid mice which are radically immunocompromised. In direct contrast to Vierling's teachings, however, the pending claims do not encompass immunodeficient animals, which are disadvantageous because such animals cannot model immune components of disease. As such, Applicants assert that Vierling's disclosure, which relates only to immunodeficient animals, cannot teach or suggest the claimed invention.

Nevertheless, Applicants have rewritten Claim 1 to specifically recite, although already implicit in the claim language in view of the instant specification, that the host mammal has a normal immune system. Accordingly, withdrawal of the rejection of Claim 1 under 35 U.S.C. § 102(e) in view of Vierling is respectfully requested.

**Rejections Under 35 U.S.C. § 103(a)**

Claim 1 has been rejected under 35 U.S.C. § 103(a) as allegedly obvious both over Rhim et al., 1995 ("Rhim") in view of Vierling, and over International Application No. WO96/39810 to Knudsen ("Knudsen") in view of Vierling. Applicants respectfully disagree.

Undergoing the same faulty claim construction with respect to the term "tolerant," the Examiner applies certain prior art, immunocompromised model systems in an effort to meet the present invention. (Office Action at pages 5 and 7). The Examiner admits that Vierling and Knudsen teach only immunocompromised hosts – in direct contrast to the instantly claimed invention which does not encompass immunodeficient animals. Thus, neither Vierling nor Knudsen teach the claimed invention.

Moreover, nowhere does Vierling or Knudsen teach or suggest how to modify the taught immunocompromised models to then be capable of using animals having a normal immune system. In fact, the immunocompromised models of the prior art and the non-immunocompromised models of the present invention are, in practice, mutually exclusive. It remains unfeasible to convert an immunocompromised animal into one having a normal immune system. Similarly, having overcome the disadvantages of immunosuppressed models by creating a non-immunocompromised model, there would be no motivation to re-introduce those disadvantages. As such, the requisite motivation to modify the respective teachings of the cited prior art relating to immunocompromised animals to reach the presently claimed invention does not exist.

Rhim teaches colonization by rat (not human) liver cells of the liver of transgenic mice carrying urokinase, a hepatotoxic transgene under the control of a liver-specific promoter that is only active postnatally. Immunotolerance was achieved by crossing Alb-uPA transgenic mice with Swiss athymic nude mice. Thus, the introduction of the Alb-uPA transgene into an immunocompromised *nu / nu* mice does not generate a model system having a normal immune system. As such, this teaching clearly fails to disclose or suggest the combination with Vierling to produce a model animal having both a normal immune system and a liver of human hepatocytes. The Examiner points to fanciful language in Rhim ("raises the exciting possibility that [mouse livers] also can be reconstituted with human liver cells"), which if anything, evidences a long-felt need in the prior art for the model system that Applicants have invented. Indeed, given Rhim's use of athymic nude mice, any proffered combination involving Rhim simply lacks the requisite reasonable expectation of success. Furthermore, even in combination with Vierling as proposed, the combination fails to reach the claimed invention which requires a normal immune system.

As indicated above, Applicants have rewritten Claim 1 to specifically recite that the host mammal has a normal immune system, which was implicit in the original claim language as properly viewed in context of the instant specification. As such, Applicants assert that the claimed invention is not obvious in view of Vierling, Rhim, and Knudsen, either singly or in combination. Accordingly, withdrawal of the rejections of Claim 1 under 35 U.S.C. § 103(a) is respectfully requested.

## Conclusion

Applicants respectfully request reconsideration of the application, and entry of the foregoing remarks into the file history of the above-identified application. Applicants believe that in light of the foregoing amendments and remarks, all pending claims are in condition for allowance and accordingly, respectfully request withdrawal of the outstanding objections and rejections. An allowance is earnestly sought.

Respectfully submitted,

Dated: March 24, 2004

Lisa B. Kole

Lisa B. Kole
PTO Registration No. 35,225

by:

Peter J. Shen
PTO Registration No. 52,217

Attorneys for Applicant
Baker Botts, LLP
(212) 408-2595

Attachments